Complete Summary

GUIDELINE TITLE

American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition.

BIBLIOGRAPHIC SOURCE(S)

Chlebowski RT, Col N, Winer EP, Collyar DE, Cummings SR, Vogel VG 3rd, Burstein HJ, Eisen A, Lipkus I, Pfister DG. American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. J Clin Oncol 2002 Aug 1;20(15):3328-43. [119 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Prevention
Risk Assessment
Technology Assessment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To update an evidence-based technology assessment of chemoprevention strategies for breast cancer risk reduction

TARGET POPULATION

Women at risk for breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Pharmacologic Interventions for Breast Cancer Risk Reduction

1. Tamoxifen (Nolvadex)
2. Raloxifene (Evista)

   Note: The use of raloxifene to lower breast cancer risk is not recommended.

3. Aromatase inhibitor/inactivator (e.g., anastrozole [Arimidex], letrozole, exemestane)

   Note: The use of any aromatase inhibitor or aromatase inactivator to lower breast cancer risk is not recommended.

4. Retinoids (fenretinide)

   Note: The use of fenretinide to lower breast cancer risk is not recommended.

5. Use of hormone replacement therapy (HRT) in combination with tamoxifen (also considered but not recommended)

MAJOR OUTCOMES CONSIDERED

- Incidence of breast cancer
- Breast cancer-specific survival
- Overall survival
- Net health benefit

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

In 1999, a comprehensive, formal literature review was conducted with the OncoView program (Pracon) (which incorporates MEDLINE, CancerLit, and selected scientific Web sites on the Internet). The literature review sought references from 1990 to 1998 on tamoxifen, tamoxifen and breast cancer risk reduction, tamoxifen side effects and toxicity (including endometrial cancer risk), tamoxifen influences on nonmalignant diseases (including coronary heart disease and osteoporosis), and decision making by women at risk for breast cancer. A parallel search was performed for raloxifene. Of the 2,134 clinical references identified and considered, 102 are referenced in the 1999 report.

Given the emerging nature of the evidence, attempts were made to update the primary published information, particularly for the major clinical trials involving tamoxifen and raloxifene. This was done by including key investigators on the Working Group and inviting relevant corporate entities to submit the most current clinical evidence in writing.

In 2002, the literature searches were updated using MEDLINE, CancerLit, PubMed, and scientific Internet sites (selected by link frequency). References were searched from June 1999 through March 2002 using the following search terms: tamoxifen, raloxifene, aromatase inhibitors, retinoids and breast cancer, breast cancer risk reduction, and breast cancer risk communication. Of the 3,733 references identified and reviewed at least by title, 119 are referenced in the 2002 report.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Technology assessment is defined as a process for determining whether a procedure is appropriate for broad-based conventional use in clinical practice. The process used in this technology assessment followed defined American Society of Clinical Oncology (ASCO) policies and procedures; these policies and procedures are similar to those published in the documents "Outcomes of Cancer Treatment

for Technology Assessment and Cancer Treatment Guidelines" and "Clinical Practice Guidelines for the Use of Tumor Markers in Breast and Colorectal Cancer."

In 1999, the working group identified specific questions to be addressed by the technology assessment, developed a strategy for completing the technology assessment, and reviewed the available literature and evidence. The technology assessment Working Group developed a series of questions about breast cancer risk-reduction strategies with tamoxifen and raloxifene. The questions listed below were answered after a review of the relevant evidence for each drug in the report:

- Is there strong or credible evidence to conclude that tamoxifen or raloxifene will reduce the risk of developing breast cancer?
- Is there strong or credible evidence to conclude that tamoxifen or raloxifene will reduce the risk of dying from breast cancer for women who do not have breast cancer?
- Is there strong or credible evidence to conclude that there is a net health benefit and improvement in overall survival associated with tamoxifen or raloxifene use for women who do not have breast cancer if taken to reduce the risk of this disease?

In addition, the effective and responsible communication by physicians of issues regarding breast cancer risk reduction to women considering use of these agents was also addressed on a preliminary basis.

In 2002, the working group reviewed the recommendations made in the original 1999 technology assessment in light of new evidence on breast cancer chemoprevention.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Consensus Development Based on Evidence

1999: The working group identified specific questions to be addressed by the technology assessment, developed a strategy for completing the technology assessment, and reviewed the available literature and evidence. The process included three face-to-face meetings of available working group members over a 4-month period and circulation of primary information and draft forms of the technology assessment to all working group members, with opportunity to comment.

2002: The working group reviewed the literature and, in a series of meetings and conference calls, considered recommendations from the original 1999 technology assessment.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developer reviewed published cost analyses. One study, a cost-effectiveness analysis based on tamoxifen effects seen in P-1 over 5 years, found tamoxifen use to be cost-effective overall, considering all medical event–related costs compared with no tamoxifen use. The principal outcome of that study was cost per life-year gained. The principal outcome of two additional studies, that used the Markov modeling of clinical outcomes, were quality-adjusted live expectancy and cost-effectiveness. The guideline developers comment only on the quality-adjusted survival predictions of these studies.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The technology assessment satisfied American Society of Clinical Oncology (ASCO) policy-defined internal review procedures. The content of the technology assessment and the resulting manuscript were reviewed and approved by the Health Services Research Committee (HSRC) and by the American Society of Clinical Oncology Board of Directors before dissemination.

The recommendations of this technology assessment update regarding tamoxifen and raloxifene are in substantive agreement with two recently published guidelines from other agencies generated under slightly different time frames:

- "Chemoprevention of breast cancer: A joint guideline from the Canadian Task Force on Preventive Health Care and the Canadian Breast Cancer Initiative´s Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer."
- "NCCN Breast Cancer Risk Reduction Guideline: The Complete Library of NCCN Oncology Practice Guidelines." National Comprehensive Cancer Network.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Tamoxifen

For women with a 5-year projected breast cancer risk of $\geq$1.66%, tamoxifen (at 20 mg/d for 5 years) may be offered to reduce risk. Consideration of tamoxifen is appropriate for the goal of lowering the short-term risk of developing breast cancer. Risk/benefit models suggest that greatest clinical benefit with least side effects are derived from use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women

without a uterus, and women at higher breast cancer risk. Data do not as yet suggest that tamoxifen provides an overall health benefit or increases survival.

Risk/benefit calculation for tamoxifen use is challenging. There is no simple scale to weigh the disparate clinical outcomes that vary in their morbidity and mortality risk. To inform potential tamoxifen users, the relative risk of outcomes under tamoxifen influence needs to be translated into absolute terms for each woman. In all circumstances, tamoxifen use should be discussed as part of an informed decision-making process with careful consideration of risks and benefits.

Raloxifene

Use of raloxifene to lower breast cancer risk is not recommended. Raloxifene should be reserved for its approved indication to prevent or treat bone loss in postmenopausal women.

Aromatase Inhibitor/Inactivators

Use of any aromatase inhibitor or aromatase inactivator to lower breast cancer risk is not recommended.

Retinoids

Use of fenretinide to lower breast cancer risk is not recommended.

Other Issues

Clinical trials evaluating potential chemoprevention agents either alone or in combination are encouraged.

Placebo controls are appropriate for breast cancer risk reduction trials since no intervention has been demonstrated to have a favorable impact on net health or survival.

Use of tamoxifen in combination with hormone replacement therapy (HRT) outside of a clinical trial setting is not recommended given the uncertainty regarding long-term side effects of the combination and the association of hormone replacement therapy with increased breast cancer risk in observational studies.

Use of tamoxifen for breast cancer risk reduction in combination or sequentially with other agents (such as raloxifene or aromatase inhibitors) has either not been studied or studies have yet to be reported.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based primarily on published randomized trials. In addition, testimony was collected from invited experts and interested parties.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Tamoxifen

- A meta-analysis of data from four randomized tamoxifen trials with updated results for three European trials identified a 38% reduction in breast cancer with tamoxifen (odds ratio, 0.62; 95% Confidence Interval, 0.42 to 0.89). These results support a significant influence of tamoxifen on reducing short-term breast cancer risk. The Early Breast Cancer Trialists Cooperative Group (EBCTCG) showed a 47% reduction in relative risk of contralateral breast cancer was associated with 5 years of tamoxifen use (Relative Risk, 0.53; Standard Deviation, 0.09; P<.00001), providing further support for a tamoxifen effect on new breast cancer development. This trial also showed that five years of tamoxifen substantially reduced the risk for breast cancer recurrence and contralateral cancer that persisted for 5 to 10 years after termination of tamoxifen use.
- Tamoxifen reduced breast cancer risk in women with BRCA2 mutations in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, in whom tumors were largely receptor-positive (Relative Risk, 0.38; 95% Confidence Interval, 0.06 to 1.56).
- Tamoxifen was associated with a modest, nonsignificant reduction in fractures compared with placebo in the National Surgical Adjuvant Breast and Bowel Project P-1 trial and with significantly fewer fractures compared with anastrozole in an adjuvant trial.

Subgroups Most Likely to Benefit:

Risk/benefit models suggest that greatest clinical benefit with least side effects is derived from use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus, and women at higher breast cancer risk.

POTENTIAL HARMS

Tamoxifen

- Tamoxifen increases endometrial cancer risk in postmenopausal women with a uterus by approximately two- to four-fold. The Early Breast Cancer Trialists Cooperative Group (EBCTCG) showed an increased risk of endometrial cancer with use of tamoxifen. Tamoxifen-associated excess mortality related to endometrial cancer was approximately one death per 1,000 postmenopausal women with a uterus treated. (Recommended follow-up for women receiving tamoxifen includes a yearly gynecologic examination and timely work-up of vaginal bleeding.)
- Tamoxifen use is associated with more frequent hot flashes and vaginal discharge.

- Development of cataracts is more frequent (Relative Risk, 1.14; 95% Confidence Interval, 1.01 to 1.29) with tamoxifen use, with the absolute risk increasing by 3 per 1,000 women.
- A recent meta-analysis of published tamoxifen trials found the incidence of both venous thromboembolic events and strokes to be significantly greater in women receiving tamoxifen.
- Although a meta-analysis of randomized trials identified increased gastrointestinal and colorectal malignancies associated with tamoxifen use, a nested case-control study found no increase in colorectal cancer among tamoxifen users, so the issue remains unsettled.

Subgroups Most Likely to be Harmed:

African-American women are anticipated to have less tamoxifen benefit based largely on increased risk of a vascular event and lower fracture risk.

CONTRAINDICATIONS

CONTRAINDICATIONS

Tamoxifen use for breast cancer risk reduction is relatively contraindicated and not recommended in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- A full discussion of the risks and benefits of hormone replacement therapy (HRT) is beyond the scope of this current technology assessment. This technology assessment takes no position regarding hormone replacement therapy use in postmenopausal women. However, recommendation of hormone replacement therapy use for cardiovascular disease risk reduction and overall health or survival benefit should be approached using the same risk/benefit algorithm outlined for tamoxifen.
- With regard to breast cancer risk assessment in the future, additional diagnostic and laboratory tests are being evaluated for breast cancer risk assessment. They include bone density, mammographic breast density, circulatory estradiol levels, and breast cells collected by a variety of techniques. The role of these procedures in clinical practice is beyond the scope of the present technology assessment.
- Women typically overestimate their risk of breast cancer, emphasizing the importance of effective communication of breast cancer risk in this setting. Relative risk describes the ratio of the risk of disease in one group compared with that in another, does not take into consideration a person´s baseline risk, and does not describe the magnitude of the absolute risk. Absolute risk varies according to baseline level of risk and could be very small when the disease is uncommon. Overall, women should be given information that presents the risks and benefits of any intervention using both absolute and relative terms.

- Women deciding on tamoxifen therapy need to consider its effects (both beneficial and harmful) on several outcomes over an extended time horizon. In sum, the communication of tamoxifen´s risks and benefits should include both absolute and relative information over a relevant time period. Attention should be paid to how the information is framed and presented.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Chlebowski RT, Col N, Winer EP, Collyar DE, Cummings SR, Vogel VG 3rd, Burstein HJ, Eisen A, Lipkus I, Pfister DG. American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. J Clin Oncol 2002 Aug 1;20(15):3328-43. [119 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 (revised 2002 Aug)

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

GUIDELINE COMMITTEE

2002 American Society of Clinical Oncology Risk Reduction Update Working Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Expert Panel Members: Rowan T. Chlebowski, MD, PhD (Co-Chair), Harbor UCLA Medical Center; Deborah Collyar (Co-Chair), Patient Advocates in Research; Susan Braun, Susan G. Komen Breast Cancer Foundation (Patient Representative); Harold J. Burstein, MD, PhD, Dana-Farber Cancer Institute; Nananda F. Col, MD, Brigham and Women´s Hospital; Steven R. Cummings, MD, University of California; Andrea Eisen, MD, Hamilton Regional Cancer Centre-McMaster University; Alexander Kennedy, MD, Cleveland Clinic; Issac Lipkus, PhD, Duke Medical Center; David G. Pfister, MD, Memorial Sloan-Kettering Cancer Center; Roxann L. Powers, MD, RCB Health Science Center; Ted P. Szatrowski, MD, Hoffman LaRoche Laboratories; Ann E. Taylor, MD, Harvard Medical School; Victor G. Vogel III, MD, Magee-Women´s Hospital UPMC

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the expert panel complied with American Society of Clinical Oncology (ASCO) policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Co-Chairs of the working group, the Chair of the Health Services Research Committee (HSRC), and the Director of the ASCO Health Services Research Department reviewed the disclosures on a case-by-case basis.

2002 ASCO Risk Reduction Upgrade Working Group

Rowan T. Chlebowski, MD, PhD, Co-Chair
Harbor UCLA Medical Center, Torrance, CA
Medical Oncology
Received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from AstraZeneca, Novartis, and Pharmacia; a consultant within the past 2 years for AstraZeneca

Deborah Collyar, Co-Chair, Patient Advocates in Research
Blackhawk, CA
Patient Representative
No conflicts noted

Susan Braun, Susan G. Komen Breast Cancer Foundation
Dallas, TX
Patient Representative
No conflicts noted

Harold J. Burstein, MD, PhD, Dana-Farber Cancer Institute
Boston, MA
Medical Oncology
A consultant within the past 2 years for AstraZeneca

Nananda F. Col, MD, Brigham and Women´s Hospital
Chestnut Hill, MA
Internal Medicine/Prevention
No conflicts noted

Steven R. Cummings, MD, University of California
San Francisco, CA
Epidemiology
Received research funding from Eli Lilly and Pfizer

Andrea Eisen, MD, Hamilton Regional Cancer Centre–McMaster University,
Hamilton, Ontario, Canada
Medical Oncology
No conflicts noted

Alexander Kennedy, MD, Cleveland Clinic, Cleveland, OH
Gynecologic Oncology
No conflicts noted

Issac Lipkus, PhD, Duke Medical Center, Durham, NC
Social/Health Psychology
No conflicts noted

David G. Pfister, MD, Memorial Sloan-Kettering Cancer Center, New York, NY,
Medical Oncology
A consultant within the past 2 years for Elan, Aventis, and
Onyx; received research funding from Imclone

Roxann L. Powers, MD, RCB Health Science Center
Morgantown, WV
Internal Medicine
No conflicts noted

Ted P. Szatrowski, MD, Hoffman LaRoche Laboratories
Nutley, NJ
Medical Oncology/Hematology/Biostatistics
No conflicts noted

Ann E. Taylor, MD, Harvard Medical School, Boston, MA
Endocrinology
Employed by Pfizer

Victor G. Vogel III, MD, Magee-Women´s Hospital UPMC
Pittsburgh, PA
Medical Oncology
Consultant for the National Cancer Institute and Cytyc Corporation; received

research funding from the National Cancer Institute (National Surgical Adjuvant Breast and Bowel Project); received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from AstraZeneca, Eli Lilly, Novartis, and Pharmacia

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: J Clin Oncol 1999 Jun;17(6):1939-55.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from American Society of Clinical Oncology, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- American Society of Clinical Oncology: Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. J Clin Oncol 14:671-679, 1996. Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.
- Chlebowski RT, Collyar DE, Somerfield MR, Pfister DG. American Society of Clinical Oncology technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. J Clin Oncol 1999 Jun;17(6):1939-55. Electronic copies: Available from the ASCO Web site.

Print copies: Available from ASCO, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

PATIENT RESOURCES

A document titled "Technology assessment: drugs to reduce breast cancer risk" is available from the American Society for Clinical Oncology (ASCO) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on February 27, 2003. The information was verified by the guideline developer on March 14, 2003.

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